Fosamprenavir

Brand Name: Lexiva
Drug Class: Protease Inhibitors

Drug Description

Fosamprenavir is the calcium phosphate ester prodrug of amprenavir, an inhibitor of HIV protease. Fosamprenavir calcium is a single stereoisomer with the (3S)(1S,2R) configuration.[1]

HIV/AIDS-Related Uses

Fosamprenavir was approved by the FDA on October 20, 2003, for the treatment of HIV-1 infection in combination with other antiretrovirals.[2]

Pharmacology

Fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate by cellular phosphatases in the gut epithelium as it is absorbed. Amprenavir binds to the active site of HIV-1 protease and prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature, noninfectious viral particles.[3]

Fosamprenavir has been studied in both healthy adult volunteers and HIV infected patients; no substantial differences in steady-state amprenavir concentrations were observed between the two populations. The time to peak amprenavir concentration (Tmax) after administration of a single dose of fosamprenavir occurred between 1.5 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after administration of fosamprenavir has not been established.[4]

When administered twice daily with ritonavir, the median maximum plasma concentration (Cmax) was 6.08 mcg/ml, the median Tmax was 1.5 hours, and the median area under the concentration-time curve (AUC) was 79.2 mcg hour/ml.[5]

In vitro, amprenavir is approximately 90% bound to plasma proteins, with concentration-dependent binding observed over the concentration range of 1 to 10 mcg/ml. Fosamprenavir primarily binds to alpha1-acid glycoprotein. Higher amounts of unbound amprenavir present as amprenavir serum concentrations increase. The partitioning of amprenavir into erythrocytes is low but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.[6]

Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The two major metabolites result from the oxidation of the tetrahydrofuran and aniline moieties. The plasma elimination half-life of amprenavir is approximately 7.7 hours. Excretion of unchanged amprenavir in the urine and feces is minimal.[7]

Fosamprenavir is in FDA Pregnancy Category C. It is not known whether amprenavir crosses the human placenta; however, it does cross the placenta in rats.[8] There are no adequate and well-controlled studies to date using the drug in pregnant women. Fosamprenavir should be used during pregnancy only when clearly needed. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including fosamprenavir. Physicians may register patients by calling 1-800-258-4263 or at the following web site: http://www.APRegistry.com. It is not known whether amprenavir is distributed into human milk; however, it is distributed into milk in rats. Because of both the potential for HIV transmission and for serious adverse reactions in nursing infants, women should be instructed not to breastfeed if they are taking fosamprenavir.[9]

HIV-1 isolates with a decreased susceptibility to amprenavir have been selected in vitro and obtained from patients treated with fosamprenavir. Amprenavir resistance-associated mutations at positions I54L/M, V32I, I47V, and M46I have been detected in HIV isolates from antiretroviral-naive patients treated with fosamprenavir. No such mutations were detected in one clinical study of antiretroviral-naive patients treated with fosamprenavir/ritonavir.[10]

Adverse Events/Toxicity

The most common adverse effects associated with

Fosamprenavir

Adverse Events/Toxicity (cont.)

fosamprenavir use include hypertriglyceridemia, skin rash, depressive or mood disorders, hyperglycemia, nausea, abdominal pain, diarrhea, fatigue, headache, and vomiting.[11]

In clinical studies, 19% of patients treated with fosamprenavir developed skin rash. Most rashes were of mild to moderate intensity; fewer than 1% of patients receiving fosamprenavir developed a severe or life-threatening rash (Grade 3 or 4), including Stevens-Johnson syndrome. Fosamprenavir should be discontinued in patients with severe or life-threatening rash or with moderate rash accompanied by systemic reactions.[12]

There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors (PIs). In some patients additional factor VIII was required. In many of the reported cases, treatment with PIs was continued or restarted. A causal relationship between PI therapy and these episodes has not been established.[13]

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including fosamprenavir. During the initial phase of combination antiretroviral treatment, a patient whose immune system improves may develop an inflammatory response to indolent or residual opportunistic infections, such as Mycobacterium avium infection, cytomegalovirus infections, Pneumocystis jirovecii pneumonia, or tuberculosis. Symptoms of immune reconstitution syndrome necessitate further evaluation and treatment.[14]

Redistribution of body fat, peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy.[15]

Treatment with amprenavir alone or in combination with ritonavir has resulted in increases in the concentration of total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed prior to initiation of amprenavir therapy and at periodic intervals during treatment. Lipid disorders should be managed as clinically appropriate.[16]

Drug and Food Interactions

Fosamprenavir may be taken with or without food.[17]

Concomitant use of fosamprenavir with certain drugs that are highly dependent on CYP3A4 for clearance may raise the plasma levels of these drugs, potentially resulting in serious or life-threatening events. Drugs that are contraindicated with amprenavir include bepridil, cisapride, dihydroergotamine, ergonovine, ergotamine, methylergonovine, midazolam, pimozide, and triazolam. Rifampin is a potent inducer of CYP3A4 and can markedly reduce plasma concentrations of fosamprenavir. If fosamprenavir is coadministered with ritonavir, flecainide and propafenone are also contraindicated.[18]

Fosamprenavir should not be coadministered with delavirdine, because it may lead to loss of virologic response and possible resistance to delavirdine. Concurrent use of efavirenz or nevirapine with fosamprenavir may decrease amprenavir concentration.[19] Decreased concentrations of fosamprenavir were observed when fosamprenavir and saquinavir were taken concurrently; the effect of fosamprenavir on saquinavir has not yet been established.[20]

Concomitant use of products containing St. John's wort (Hypericum perforatum) with fosamprenavir or other PIs is not recommended. St. John's wort is expected to substantially decrease drug plasma levels and may lead to loss of virologic response and possible resistance to fosamprenavir or other PIs.[21]

Serious or life-threatening events can occur if amprenavir is taken with amiodarone, lidocaine, tricyclic antidepressants, and quinidine. Patients receiving amprenavir concomitantly with any of these drugs should be carefully monitored.[22]

Caution should be used when prescribing sildenafil in patients receiving PIs, including fosamprenavir. Coadministration of a PI with sildenafil is expected to substantially increase sildenafil concentrations and, possibly, sildenafil-associated adverse effects, including hypotension, visual changes, and priapism.[23]

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Drug and Food Interactions (cont.)

Concomitant use of fosamprenavir with certain other drugs may significantly increase or decrease plasma concentrations of amprenavir or of the coadministered drug. Adjustment in dosage or regimen should be considered when amprenavir is coadministered with antacids, ketoconazole, itraconazole, and rifabutin.[24]

Concomitant use of fosamprenavir and oral or other contraceptives containing ethinyl estradiol/norethindrone may lead to loss of virologic response. Alternative methods of nonhormonal contraception are recommended.[25]

Fosamprenavir is a sulfonamide. The potential for cross-sensitivity between other sulfonamides and amprenavir is unknown. Amprenavir should be used with caution in patients with a known sulfonamide allergy.[26]

Fosamprenavir may increase serum concentrations of warfarin when these two drugs are taken together.[27]

Contraindications

Fosamprenavir is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to amprenavir.[28]

Fosamprenavir should be used with caution in patients with a known sulfonamide allergy. Fosamprenavir contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and fosamprenavir is unknown.[29]

Clinical Trials

For information on clinical trials that involve Fosamprenavir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Fosamprenavir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[30]

Dosage Form: Tablets containing fosamprenavir 700 mg.[31]

The recommended dose of fosamprenavir for treatment-naive adult patients is either 1) 1,400 mg twice daily without ritonavir, 2) 1,400 mg once daily plus ritonavir 200 mg once daily, or 3) 700 mg twice daily plus ritonavir 100 mg twice daily. The recommended dose of fosamprenavir for PI-experienced adult patients is 700 mg twice daily plus ritonavir 100 mg twice daily. An additional 100 mg/day of ritonavir is recommended when efavirenz is administered with fosamprenavir/ritonavir once daily.[32]

In patients with mild or moderate hepatic impairment (Child-Pugh score of 5 to 8), a fosamprenavir dosage of 700 mg twice daily without ritonavir is recommended. Fosamprenavir should not be used in patients with severe hepatic impairment (Child-Pugh score of 9 to 12), since the dose of fosamprenavir cannot be reduced below 700 mg.[33]

Safety and efficacy for pediatric dosing have not been established.[34]

Storage: Store at 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F).[35]

Chemistry

CAS Name: Carbamic acid, [(1S,2R)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)-2-(phosphonooxy)propyl]-, C-[(3S)-tetrahydro-3-furanyl] ester, calcium salt[36]

CAS Number: 226700-81-8[37]

Molecular formula: C25-H34-Ca-N3-O9-P-S[38]

C48.2%, H5.5%, N6.7%, O23.1%, P5.0%, S5.1%, Ca6.4%[39]

Molecular weight: 623.64[40]

Physical Description: White to cream-colored solid.[41]

Solubility: Approximately 0.31 mg/ml in water at 25 C.[42]

Fosamprenavir

Other Names

GW433908[43]

f-APV[44]

Fosamprenavir calcium[45]

GW 433908[46]

VX 175[47]

Telzir[48]

Further Reading

Arvieux C, Tribut O. Amprenavir or fosamprenavir plus ritonavir in HIV infection: pharmacology, efficacy and tolerability profile. Drugs. 2005;65(5):633-59. Review.

Chapman TM, Plosker GL, Perry CM. Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. Drugs. 2004;64(18):2101-24. Review.

Vierling P, Greiner J. Prodrugs of HIV protease inhibitors. Curr Pharm Des 2003;9(22):1755-70.

Wire MB, Shelton MJ, Studenberg S. Fosamprenavir : clinical pharmacokinetics and drug interactions of the amprenavir prodrug. Clin Pharmacokinet. 2006;45(2):137-68.

Wood R, Arasteh K, Stellbrink HJ, et al. Six-week randomized controlled trial to compare the tolerabilities, pharmacokinetics, and antiviral activities of GW433908 and amprenavir in human immunodeficiency virus type 1-infected patients. Antimicrob Agents Chemother 2004 Jan;48(1):116-23.

Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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References

1. FDA - Lexiva Prescribing Information, 03/10/06, p. 1. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

2. FDA - Drugs Used in the Treatment of HIV Infection. Available at: http://www.fda.gov/oashi/aids/virals.html. Accessed 04/13/06.

3. USP DI - 2005; p. 1489

4. FDA - Lexiva Prescribing Information, 03/10/06, p. 3. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

5. FDA - Lexiva Prescribing Information, 03/10/06, p. 4. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

6. FDA - Lexiva Prescribing Information, 03/10/06, pp. 4-5. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

7. FDA - Lexiva Prescribing Information, 03/10/06, p. 5. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

8. USP DI - 2005; p. 1490

9. FDA - Lexiva Prescribing Information, 03/10/06, p. 22. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

10. FDA - Lexiva Prescribing Information, 03/10/06, p. 2. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

11. USP DI - 2005; p. 1491

12. FDA - Lexiva Prescribing Information, 03/10/06, p. 23. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

13. FDA - Lexiva Prescribing Information, 03/10/06, p. 15. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

14. FDA - Lexiva Prescribing Information, 03/10/06, p. 15. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

15. FDA - Lexiva Prescribing Information, 03/10/06, p. 15. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

16. FDA - Lexiva Prescribing Information, 03/10/06, p. 15. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

17. USP DI - 2005; p. 1492

18. USP DI - 2005; pp. 1490-1

19. USP DI - 2005; p. 1490

20. USP DI - 2005; p. 1491

21. USP DI - 2005; p. 1491

22. USP DI - 2005; p. 1490

23. USP DI - 2005; p. 1491

24. USP DI - 2005; pp. 1490-1

25. USP DI - 2005; p. 1491

26. USP DI - 2005; p. 1489

27. USP DI - 2005; p. 1491

28. FDA - Lexiva Prescribing Information, 03/10/06, p. 13. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

29. FDA - Lexiva Prescribing Information, 03/10/06, pp. 14-5. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

30. AHFS Drug Information - 2005; p. 634

31. AHFS Drug Information - 2005; p. 634

32. FDA - Lexiva Prescribing Information, 03/10/06, pp. 25-6. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

33. FDA - Lexiva Prescribing Information, 03/10/06, p. 26. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

34. AHFS Drug Information - 2005; p. 632

35. FDA - Lexiva Prescribing Information, 03/10/06, p. 26. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

36. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 04/13/06.

37. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 04/13/06.

38. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 04/13/06.

39. Calculation. -

40. USPD - 2005; p. 391

41. FDA - Lexiva Prescribing Information, 03/10/06, p. 1. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

42. FDA - Lexiva Prescribing Information, 03/10/06, p. 1. Available at: http://www.fda.gov/cder/foi/label/2006/021548s007lbl.pdf. Accessed 04/13/06.

43. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 04/13/06.

44. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection - MMWR 2002;51 (No.RR-7) Updated as a Living Document on November 3, 2005. Available at: http://aidsinfo.nih.gov/

45. USPD - 2005; p. 391

46. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 04/13/06.

47. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 04/13/06.

48. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. Accessed 04/13/06.